Fragmented Surface ECG Was a Poor Predictor of Appropriate Therapies in Patients with Chagas' Cardiomyopathy and ICD Implantation (Fragmented ECG in CHAgas' Cardiomyopathy Study)

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Background: Main causes of death in chronic Chagas' cardiomyopathy (CChC) are progressive congestive heart failure and sudden cardiac death. Implantable cardioverter defibrillators (ICD) have been proved an effective therapy to prevent sudden death in patients with CChC. Identification of predictors of sudden death remains a challenge.

Objective: To determine whether surface fragmented ECG (fQRS) helps identifying patients with CChC and ICDs at higher risk of presenting appropriate ICD therapies.

Methods: Multicenter retrospective study. All patients with CChC and ICDs were analyzed. Clinical demographics, surface ECG, and ICD therapies were collected.

Results: A total of 98 patients were analyzed. Another four cases were excluded due to pacing dependency. Mean age was 55.5 ± 10.4 years, male gender 65%, heart failure New York Heart Association class I 47% and II 38%. Mean left ventricular ejection fraction (LVEF) $39.6 \pm 11.8\%$. The indication for ICD was secondary prevention in 70% of patients. fQRS was found in 56 patients (59.6%). Location of fragmentation was inferior (57.1%), lateral (35.7%), and anterior (44.6%). Rsr pattern was the more prevalent (57.1%). Predictors of appropriate therapy in the multivariate model were: increased age ($P = 0.01$), secondary prevention indication ($P = 0.01$), ventricular pacing $>50\%$ of the time ($P = 0.004$), and LVEF $<30\%$ ($P = 0.01$). The presence of fQRS did not identify patients at higher risk of presenting appropriate therapies delivered by the ICD ($P = 0.87$); regardless of QRS interval duration.

Conclusions: fQRS is highly prevalent among patients with CChC. It has been found a poor predictor of appropriate therapies delivered by the ICD in this population.

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Chagas' disease; fragmented ECG; sudden death; implantable cardioverter defibrillator; ventricular arrhythmias

¹See Appendix.

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Conflicts of interest: none.

INTRODUCTION

Chagas' disease is an endemic disease in Latin America caused by a unicellular parasite, the *Trypanosoma cruzi*. Around 18 million of people are infected and almost 25% of them will develop chronic myocardial disease after years or decades.¹

After an asymptomatic period, chronically infected individuals develop chronic myocarditis and less frequently megacolon, megaesophagus, or neurological afflictions.² The main causes of death in chronic Chagas' cardiomyopathy (CChC) are progressive congestive heart failure and sudden cardiac death.^{3,4} Chagas' disease has become a worldwide problem, given the new immigration patterns. Physicians around the world should become aware of its existence and how to recognize and treat it.⁵

Implantable cardioverter defibrillators (ICDs) have been proven to be effective in reducing sudden death due to malignant ventricular arrhythmias in patients with CChC.⁶⁻⁸ As economical resources for funding such as expensive therapy are limited in Latin America, it is of utmost importance to determine which patients are at a higher risk. Prior studies have identified older age and low ejection fraction as predictors of sudden death or appropriate therapies delivered by the ICD.⁹ Increased number of shocks delivered by the ICD has also been identified as a predictor of cardiovascular mortality.¹⁰

Fragmented surface ECG (fQRS) has been recently described as an easy and handy method to predict the risk of total and arrhythmic death in patients with coronary artery disease (CAD).¹¹⁻¹³

The aim of this study is to determine whether fQRS is a predictor of appropriate therapies delivered by the ICD in patients with CChC.

METHODS

The present study was a retrospective cohort study of patients with CChC and an ICD for primary or secondary prevention of sudden cardiac death at 14 Latin America centers from January 2000 to November 2011.

The inclusion criteria were CChC, diagnosed by positive serologic tests and classic criteria including: living in endemic areas, ECG, and chest

x-ray criteria and an ICD implanted for primary or secondary prevention of sudden cardiac death. The ethics committee of each institution approved the study.

ECG Analysis

All preimplant ECGs were blindly reviewed at a core lab center in Queen's University by two independent investigators (AB, RM). Disagreement was solved by consensus. The definition of fQRS was QRS complexes with the presence of an additional R wave (R') or notching in the nadir of the R wave or the S wave, or the presence of >1 R' (fragmentation) in two contiguous leads, corresponding to a major coronary territory.^{11,13} Additionally, for QRS complexes of typical right/left bundle branch block (≥ 120 ms) fQRS was defined as a QRS complex with >2 R' waves or notches in the R or S wave in two contiguous leads.^{11,13} Surface 12-lead ECGs were recorded at the original centers (frequency range 0.15–150 Hz, 25 mm/s, 10 mm/mV). The ECGs were scanned at 300 DPI resolution saved as a JPEG and emailed to the central core lab.

ICD Programming and Therapies

The ICD programming included therapy for standard ventricular tachycardia (VT) with antitachycardia pacing (ATP) combined with low-energy shock therapy and for ventricular fibrillation (VF) shock therapy using a 300 ms cutoff cycle interval.

ICD therapy was classified as appropriate or inappropriate (from dot plots and stored EGMs) by a blind independent expert panel in the Queen's core lab (Kingston, Ontario, Canada). Therapies were considered inappropriate when the ICD delivered them for any rhythm rather than VT/VF.

Outcomes

The primary outcome was appropriate therapies delivered by the ICD (shocks/ATP). Secondary outcomes were time to first appropriate therapy and inappropriate therapies.

A total of 102 patients were initially included. Four patients were excluded from the analysis due to permanent pacing rhythm. Groups were divided into fQRS, non-fQRS, wide complex fQRS (WfQRS), and wide complex non-fQRS.

Table 1. Baseline Characteristics of Patients

Baseline Characteristics	Total Group n = 98	fQRS n = 56	Non-fQRS n = 42	P-value
Age (years $\pm$ DS)	55.5 $\pm$ 10.4	57.2 $\pm$ 16.1	54.1 $\pm$ 9.6	NS
Male sex (%)	63 (65%)	37 (66%)	26 (62%)	NS
LVEF (ECHO, %)	39.6 $\pm$ 11.8	34.4 $\pm$ 8.9	42.8 $\pm$ 12.2	0.041
QRS duration (ms)	145 $\pm$ 88	156 $\pm$ 94	141 $\pm$ 74	0.039
QRS > 120 ms	50 (51%)	30 (53%)	20 (48%)	NS
Functional capacity (%)				
I	46 (47%)	26 (46%)	20 (48%)	NS
II	37 (38%)	20 (36%)	17 (40%)	
III	15 (15%)	9 (16%)	6 (14%)	
Atrial fibrillation	16 (16%)	10 (18%)	6 (14%)	NS
Primary prevention ICD	29 (30%)	18 (62%)	11 (38%)	NS
Secondary prevention ICD	69 (70%)	39 (56%)	30 (44%)	NS
Pacing > 50%	36 (37%)	20 (36%)	16 (38%)	NS
Appropriate therapy	57 (58%)	33 (59%)	24 (57%)	NS
Time to first therapy (months)	8.4 $\pm$ 19	7.4 $\pm$ 22	9.9 $\pm$ 9	NS
Inappropriate Therapy	20 (20%)	13 (23%)	7 (17%)	NS
Medical treatment				
Amiodarone	68 (69%)	40 (71%)	28 (67%)	NS
β -Blockers	64 (65%)	42 (75%)	22 (52%)	0.03
ARB, IECA	43 (43%)	25 (45%)	18 (43%)	NS
Spironolactone	27 (28%)	16 (29%)	11 (26%)	NS

Statistical Analysis

Data were collected in an Excel (Microsoft, Redmond, WA, USA) spreadsheet and imported into IBM SPSS version 19.0 (Armonk, NY, USA) for statistical analysis. Data were initially analyzed descriptively, including means and standard deviations for continuous data, and frequencies and percentages for categorical data.

The associations between narrow/wide QRS and patient characteristics, appropriate therapy, inappropriate shock, and death were assessed using the chi-square test (Pearson or Fisher's exact as appropriate). The associations with age and left ventricular ejection fraction (LVEF) were assessed using the independent samples *t*-test; its association with time between implant and therapy was assessed using the Mann-Whitney U. The associations between the four-level variable and the same characteristics and outcomes were examined using the Pearson chi-square test, the one-way ANOVA, and the Kruskal-Wallis test.

Variables that had a potentially significant association with the outcomes ($P < 0.15$) were entered into a series of multivariable logistic regressions to attain final models containing the subset of statistically significant variables. The time between implant and therapy was log-transformed, and multivariable linear regression was used to

develop a final model. Kaplan-Meier curves were also developed to assess the association between QRS (split at 120 as above), fractionation, and the four-level QRS/fractionation variable, with the outcomes of time between implant and therapy, and time to death.

RESULTS

We analyzed 98 patients, all of them with CChC and ICD. Mean follow-up was 33 ± 20 months. Mean age was 55.5 ± 10.4 years, male gender 65%, heart failure New York Heart Association, class I 47%, and II 38%. Mean left ventricular ejection fraction measured by echocardiogram was $39.6 \pm 11.8\%$. The indication for ICD was secondary prevention ICD in 70% of patients (Table 1). Devices implanted were single chamber 32%, dual chamber 64%, and resynchronization therapy 4%.

Patients with fQRS presented lower EF compared with non-fQRS ($34.4 \pm 8.9\%$ vs $42.8 \pm 12.2\%$, $P = 0.041$), and wider QRS (156 ± 94 ms vs 141 ± 74 ms; $P = 0.039$), and higher number of patients treated with β -blockers (42 vs 22 patients, $P = 0.03$).

ECG analysis can be seen in Table 2. fQRS was found in 56 patients (59.6%). Location of the ECG fragmentation was inferior in 57.1%, lateral in 35.7%, and anterior in 44.6%. Rsr pattern

Table 2. Electrocardiographic Characteristics

ECG Analysis	
RBBB	39 (40%)
LBBB	9 (9%)
QRS width (ms)	145 ± 88
PR	192 ± 50
QT Interval	447 ± 57
fQRS (patients,%)	56 (57.1%)
fQRS Inferior	57%,
fQRS Anterior	35%
fQRS Lateral	44%
fQRS in two or more areas	30%
fQRS pattern Rsr'	56 (57.1%)

was the more prevalent of the fragmented ECG morphologies (57.1%).

Predictors of appropriate therapy in a multivariate model were increased age (>60 years, HR 2.01, 95% CI 1.13–4.07, $P = 0.01$), secondary prevention indication for the ICD (HR 3.5, 95% CI 1.78–6.32, $P = 0.03$), ventricular pacing >50% of the time (HR 1.9, 95% CI 1.12–2.24, $P = 0.004$) and EF < 30% (HR 2.29, 95% CI 1.29–4.74, $P = 0.01$).

During the follow-up (33 ± 20 months), 57 patients (58%) presented an appropriate therapy by the ICD. The majority of the cases were due to VT (67%). The incidence of arrhythmic events were similar in fQRS group (57%) and non-fQRS (56%), $P = 0.2$.

The presence of fQRS did not identify patients at higher risk of presenting appropriate therapies delivered by the ICD (HR 1.4, 95% CI 0.84–2.05, $P = 0.87$, Fig. 1, panel A); regardless of QRS interval duration (Fig. 1, panel B).

During the follow-up, nine patients (20%) presented inappropriate therapies. Multivariate analysis showed that paroxysmal atrial fibrillation (HR 2.4, 95% CI 1.2–3.6, $P = 0.01$) and QRS > 150 ms (HR 1.6, 95% CI 1.1–2.3, $P = 0.04$) increased the risk of inappropriate therapies. β -Blocker therapy was protective (HR 0.93, 95% CI 0.84–0.97, $P = 0.04$).

DISCUSSION

Optimal predictors of arrhythmic events in CChC population remain a challenge. The major finding of our study is that fQRS in patients with CChC did not predict an arrhythmic event in patients who receive an ICD for primary or secondary prophylaxis of SCD. In our study, the

incidence of an arrhythmic event was similar in fQRS and non-fQRS groups during a mean follow-up of 33 months. We found that older age, severe LV dysfunction, ventricular pacing > 50% of the time and secondary prevention ICD are predictors of arrhythmic event in this population.

Previous studies have shown that fQRS on 12-lead ECG is a significant predictor of arrhythmic events in patients with CAD, nonischemic cardiomyopathy and in ion channel diseases like Brugada syndrome and long QT syndrome.^{11–23}

fQRS has been implicated in heterogeneous activation of the ventricles due to myocardial scar or ischemia. Indeed, fragmentation is associated to areas of slow conduction due to scar demonstrated by MRI or endocardial electrical mapping.^{24,25} Distribution and pattern of the scar depends on the disease states, in CAD, myocardial scars are segmental and subendocardial or transmural, whereas in nonischemic cardiomyopathy the scars are patchy and mid myocardial or subepicardial, predominantly in the perivalvular areas.^{12,26,27}

CChC is a chronic diffuse myocarditis with patches of fibrosis alternating with healthy myocardial tissue. It is also a dromotropic disorder with frequent involvement of the conduction system. In this particular condition, fQRS may represent a delay in the conduction of the Purkinje fibers and may not necessarily correlate with the extension of the myocardial fibrosis.^{3,28–30} Despite our study was not designed to speculate on the physiopathology of the fQRS in CChC, the above-mentioned physiopathological mechanisms may help to explain the discrepancy between our results and the results other studies in different clinical scenarios. The lack of systematic use of magnetic resonance imaging (MRI) did not allow for specific analysis. The high use of amiodarone in the whole cohort was not surprising, as amiodarone is widely used in Latin America, specifically in this population. Its relation to fQRS remains unknown. A separate comment deserves the fact that a significant higher proportion of patients with fQRS were receiving β -blockers, which could attenuate the impact of fQRS as a substrate for ventricular arrhythmias.

In our study, we found that the prevalence of fQRS in CChC patients implanted with ICDs is high (almost 60%). In patients with CAD or DCM implanted with ICDs, the prevalence

Figure 1. Panel A: Kaplan-Meier survival analysis for an arrhythmic event in fragmented QRS (fQRS) and nonfragmented QRS (non-fQRS). Panel B: Kaplan-Meier survival analysis for an arrhythmic event in patients with wide (QRS > 120 ms) or narrow QRS (QRS < 120 ms).

was lower (23%). This could be explained by the characteristic myocardial CChC myocardial disturbance but also due to a selection of a sicker population.

In our study, secondary prevention was the indication for the ICD in 70% of the cases which represents per se, a subgroup of patients with poorer heart condition. Secondary prevention was a strong predictor of arrhythmic events. It is possible that fQRS measured in earlier stages of the disease could help identifying patients at higher risk of arrhythmic events.

Limitations

Several limitations should be acknowledged. The retrospective nature of this study could introduce bias. The higher percentage of patients with secondary prevention indication may also result in bias selection. Arrhythmic events were defined by appropriate ICD therapy, which depends at least partly upon device programming and may not always reflect lifesaving therapy. The retrospective nature of this study did not allow for mortality analysis, as most of dead patients were lost in follow-up and several centers did not have access to their charts, ECGs, or ICD printed EGMs. Finally, there was a disparity of ECG filters used by different centers that could affect proper fQRS detection and MRI was not system-

atically used to validate fibrosis in patients with fQRS.

CONCLUSION

fQRS is highly prevalent among patients with CChC implanted with ICDs. fQRS has been found a poor predictor of appropriate therapies delivered by the ICD in this population.

Disclosure

None

Abbreviations list

CAD:	coronary artery disease
CChC:	chronic Chagas' cardiomyopathy
DCM:	dilated cardiomyopathy
ECG:	12-lead electrocardiogram
EF:	ejection fraction
fQRS:	fragmented QRS
ICD:	implantable cardioverter defibrillator
LV:	left ventricular
LVEF:	left ventricular ejection fraction
SCD:	sudden cardiac death
VF:	ventricular fibrillation
VT:	ventricular tachycardia
WfQRS:	wide complex fQRS

FECHA: Fragmented ECG in CHAgas' cardiomyopathy Study

APPENDIX

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